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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,583	11/14/2001	Avi J. Ashkenazi	P2730P1C7	3322

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EXAMINER

MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/993,583

Applicant(s)

ASHKENAZI ET AL.

Examiner

Joseph F Murphy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09/02/2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 121-127 and 129-131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 121-127, 129-131 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>08022004</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

Claims 121-127, 129-131 are pending and under consideration.

Response to Amendment

The objection to the Title and Specification have been obviated by Applicant's amendment and is thus withdrawn.

Applicants has provided the serial number and specific page number(s) of the parent application to which priority is desired which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession and fully enabled, thus priority to the filing date of U.S. provisional Application 60/141,037, June 23, 1999 has been granted.

The rejection of claims 119-120 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6242419 (Strachan et al), has been rendered moot by cancellation of the claims, and are thus withdrawn.

The rejection of claims 130-131 under 35 USC § 112 first paragraph as lacking enablement have been obviated by Applicant's amendment and is thus withdrawn.

The rejection of claims 130-131 under 35 USC § 112 first paragraph as lacking written description have been obviated by Applicant's amendment and is thus withdrawn.

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Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 121-123 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a full length PRO943 protein of SEQ ID NO: 119, does not reasonably provide enablement for a polypeptide at least 80-99% identical to SEQ ID NO: 119. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 119-123, 130-131 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides which will retain the characteristics of PRO943. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of PRO943. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype. Thus showing that

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even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. While the specification discloses that the PRO943 polypeptide functions in the chondrocyte redifferentiation assay, the claims do not set forth a functional limitation for the variant polypeptides. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a

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polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polypeptide variants of PRO943, and has not taught how to make polypeptide variants of PRO943, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

Applicant has added the limitation wherein the nucleic acid encoding the protein is amplified in lung or colon tumors, and argues that based on the detailed description of the cloning and expression of nucleic acid variants of PRO943 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO: 119 and the functional recitation in the instant claims, Applicants submit that one of skilled in the art would know how to make and use the claimed variants, as a lung or colon or colon tumor marker. However, the Specification only shows that the full-length nucleic acid of SEQ ID NO: 119 will serve as a marker for lung or colon cancer tumors, while the claims encompass variant polypeptides. There

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are a large number of polypeptide species encompassed by the claims, however, the Specification does not disclose the critical amino acid residues necessary to maintain the function of detecting lung or colon tumors. The specification does not disclose the correlation between the structure (sequence) of the encompassed amino acids and the function of detecting lung or colon tumors. The amino acid sequence determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the amino acids are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Therefore it would require undue experimentation by one of skill in the art to make and use the invention as claimed without further guidance from the instant specification.

In addition, Applicant has submitted declarations pursuant to 37 CFR § 1.132 by Dr. Ashkenazi and Dr. Polakis. These declarations argue that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, and that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. However, the rejections are directed to the fact that there are a large number of polypeptide species encompassed by the claims, while the Specification does not disclose the critical amino acid residues necessary to maintain the function of detecting lung or colon tumors.

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Claims 119-123, 130-131 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to polypeptides at least 80-99% identical to SEQ ID NO: 119 and are thus genus claims. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded PRO943 variants. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 119 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual

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reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant has added the limitation wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors, and argues that based on the detailed description of the cloning and expression of variants of PRO943 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequences SEQ ID NO: 119 and the functional recitation in the

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instant claims, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims.

However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function , or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as functional characteristics coupled with a known or disclosed correlation between structure and function of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed which have the claimed function. Thus, no identifying characteristics or properties of the instant polynucleotides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of SEQ ID NO: 119 is insufficient to describe the genus.

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One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Claim 121-127, 129-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of the biological material is considered necessary for the enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R. §§ 1.801-1.809). Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Applicants have provided the deposit number for the plasmid encoding PRO943, however, the specification is not fully compliant with all of the provisions for maintenance and availability of the deposited material. If a deposit is made under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g. see 961 OG 21, 1977), and Applicants, their assignee or their agent needs to provide a declaration containing the following:

- i) a statement all restrictions on the availability to the public of the deposited material so deposited will be irrevocably removed upon the granting of a patent. ii) A statement that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122. iii) A statement that the deposited material will be maintained with all of the care necessary to keep it viable and

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uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty years after the date of deposit or for the enforceable life of the patent, whichever period is longer. iv)

A statement by declarant that all statements are true and that all statements made on information and belief are believed to be true; and further that these statements were made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon. Pursuant to 37 C.F.R. § 1.804(b), when the original deposit is made after the effective filing date of an application for patent, the applicant must promptly submit a statement from a person in a position to corroborate the fact, stating that the biological material which is deposited is a biological material specifically identified in the application as filed. Furthermore, 37 C.F.R. § 1.809 sets forth that the assurance that a biological deposit will be made must come from Applicant, or, in the case of an issued patent, from the patent owner. Assurance by the attorney of record is insufficient.

Conclusion

Claims 121-127, 129-131 are rejected.

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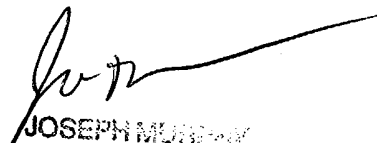
Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
November 10, 2004


JOSEPH MURPHY
PATENT EXAMINER